

REMARKS

I. Status Summary

Claims 36-63 are now pending in the subject U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 57 and 60-62 have been rejected under 35 § U.S.C. 112, second paragraph, upon the contention that the claims are indefinite.

Claims 36-42 and 45-63 have been rejected under 35 § U.S.C. 112, first paragraph, upon the contention that the claims do not comply with the written description requirement.

Claim 36 has been rejected under 35 U.S.C. § 102(e) upon the contention that the claim is being anticipated by U.S. Patent No. 7,205,283 to Yoon et al. (hereinafter "Yoon") as evidenced by Holen et al. (2003) *Nucleic Acids Research* 31:2401-2407 (hereinafter "Holen"). Claims 36-41, 43, 45-49, 52, 53, and 56-63 have been rejected under 35 U.S.C. § 102(e) upon the contention that the claims are anticipated by PCT International Patent Application Publication No. WO 2004/042024 of Reich et al. (hereinafter "Reich").

Claims 36-43 and 45-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of U.S. Patent Application Publication No. 2003/0143732 of Fosnaugh et al. (hereinafter "Fosnaugh"). Claims 36-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh, and further in view of the Ambion siRNA target finder (hereinafter "Ambion").

Claims 37, 43, 44, 60, and 61 have been canceled without prejudice. Applicants hereby reserve the right to file one or more continuation and/or divisional applications with claims directed to the subject matter of the instantly canceled claims.

Claims 36, 38, 45, and 47-51 have been amended. The amendments to claims 38, 45, and 47-51 include updating these claims to depend from claim 36 rather than canceled claim 37. Claim 38 has been further amended to recite "the sense region" and "the antisense region of the siRNA molecule" as antecedent basis for these claim elements can be found in claim 36. Claim 36 has been amended to recite the element originally recited in claims 37 and 44. Thus, support for the amendment to claim 36 can be found in claims 37 and 44 as originally presented. As such, no new matter has been added by the amendments to the claims.

New claims 64 and 65 have been added. Support for the new claims can be found throughout the specification as filed, including particularly at page 13, line 26, through page 14, line 2, and in the Sequence Listing. Thus, no new matter has been added by the inclusion of the new claims.

Reconsideration of the application as amended and in view of the Remarks presented hereinbelow is respectfully requested.

II. Response to the Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 57 and 60-62 have been rejected under 35 U.S.C. 112, second paragraph, upon the contention that the claims are indefinite. Particularly, the Patent Office asserts that claim 57 recites the element "at least one siRNA molecule of claim 36", and that there is insufficient antecedent basis for this element in claim 36 because claim 36 is directed to a single siRNA molecule.

Applicants respectfully disagree. Applicants respectfully submit that the application as filed clearly sets forth that the term "a" as in "A small interfering RNA (siRNA) molecule" as originally recited in claim 36 "refers to 'one or more' when used in this application, including the claims". See Specification at page 5, lines 5-7. As such, applicants respectfully submit that original claim 36 encompassed a plurality of siRNA molecules, and thus there is no ambiguity in claim 57 with respect to expression vectors comprising a nucleic acid sequence encoding at least one siRNA molecule of claim 36.

Furthermore, applicants respectfully submit that claim 57 also encompasses nucleic acid sequences encoding multiple copies of the siRNA molecule(s) of claim 36. With respect to these embodiments, applicants respectfully submit that one of ordinary skill in the art would thus understand claim 57 to encompass multiple copies of the siRNA molecule of claim 36. Therefore, for this additional reason, applicants respectfully submit that the instant rejection of claim 57 is believed to be improper.

Accordingly, applicants respectfully request that the instant rejection of claim 57 with withdrawn at this time. Since claims 60-62 were rejected based on their dependence from claim 57, it is further believed that the rejection as to claims 60-62 has been rendered moot.

III. Response to the Rejection under 35 U.S.C. § 112, First Paragraph

Claims 36-42 and 45-63 have been rejected under 35 U.S.C. 112, first paragraph, upon the contention that the claims do not comply with the written description requirement. Particularly, the Patent Office appears to assert that SEQ ID NOs: 1 and 3 are not a representative number of species sufficient to describe the genus of HIF-1 $\alpha$  molecules.

Without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 36 has been amended to recite *inter alia* a small interfering RNA (siRNA) molecule that down regulates expression of a human hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) gene

by RNA interference comprising a sense region and an antisense region, wherein the sense region comprises the sequence 5'-GATGACATGAAAGCACAGA-3' (SEQ ID NO: 7) and the antisense region comprises a 100% reverse-complement of SEQ ID NO: 7. Support for the amendment to claim 36 can be found in claims 37 and 44 as originally filed.

Thus, a genus of siRNAs with a particular sense region sequence has been claimed. Applicants respectfully submit that the Patent Office has conceded that "specification discloses siRNA molecules directed to SEQ ID: NO: 1...", which corresponds to human HIF-1 $\alpha$ . As such, applicants respectfully submit that the specification fully describes the subject matter of claim 36.

Furthermore, applicants respectfully submit that the Patent Office's assertions with respect to the disclosure of Reich do not support the instant rejection. Applicants respectfully submit that SEQ ID NO: 7 is 100% identical to nucleotides 649-667 of both of GENBANK® Accession Nos. NM\_001530 and NM\_181054 cited in the Non-Final Official Action, and thus the subject matter of the instant claims would be expected to down regulate the variant human HIF-1 $\alpha$ 's cited by the Patent Office.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of lack of written description of the pending claims. As a result, applicants respectfully request that the instant rejection of claims 36-42 and 45-63 under 35 § U.S.C. 112, first paragraph, be withdrawn at this time.

#### IV. Responses to the Rejections under 35 U.S.C. § 102(e)

Claim 36 has been rejected under 35 U.S.C. § 102(e) upon the contention that the claim is being anticipated by Yoon as evidenced by Holen. Claims 36-41, 43, 45-49, 52, 53, and 56-63 have been rejected under 35 U.S.C. § 102(e) upon the contention that the claims are anticipated by Reich.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

##### IV.A. Response to the Rejection over Yoon

Claim 36 has been rejected under 35 U.S.C. § 102(e) upon the contention that the claim is being anticipated by Yoon as evidenced by Holen. According to the Patent Office, Yoon teaches antisense oligonucleotides that meet the instant limitation of being a small interfering RNA, wherein the antisense oligonucleotides down regulate the expression of HIF-1  $\alpha$  (see Table 1, for example).

Applicants respectfully disagree. Applicants respectfully submit that Yoon does not disclose the subject matter of claim 36, which recites *inter alia* an siRNA molecule comprising a sense region and an antisense region, wherein the sense region comprises the sequence 5'-GATGACATGAAAGCACAGA-3' (SEQ ID NO: 7) and the antisense region comprises a 100% reverse-complement of SEQ ID NO: 7. Applicants respectfully submit that Yoon does not disclose any molecules with a sense region that comprises SEQ ID NO: 7, and thus does not support a rejection of claim 35 under 35 U.S.C. § 102(e).

Accordingly, applicants respectfully request that the instant rejection of claim 36 be withdrawn at this time.

#### IV.B. Response to the Rejection over Reich

Claims 36-41, 43, 45-49, 52, 53, and 56-63 have been rejected under 35 U.S.C. § 102(e) upon the contention that the claims are anticipated by Reich. According to the Patent Office, Reich teaches siRNA molecules that target HIF-1 a mRNA and inhibit the expression of the HIF-1 a gene via RNA interference.

Initially, applicants respectfully submit that claims 37, 43, 60, and 61 have been canceled, and thus the rejection is believed to be moot as to these claims.

Continuing with the instant rejection, applicants respectfully submit that Reich does not support a rejection of claim 36 under 35 U.S.C. § 102(e). Without acquiescing to the contentions of the Patent Office concerning Reich, applicants respectfully submit that claim 36 has been amended to recite the element originally recited in claim 44, which is not subject to this rejection.

Accordingly, applicants respectfully submit that claim 36 has been distinguished over Reich. Applicants further respectfully submit that claims 38-41, 45-49, 52, 53, 56-59, 62, and 63 all depend directly or indirectly from claim 36, and thus are also believed to be distinguished over Reich.

Therefore, applicants respectfully submit that Reich does not support a rejection of claims 36, 38-41, 45-49, 52, 53, 56-59, 62, and 63 under 35 U.S.C. § 102(e). As a result, applicants respectfully request that the instant rejection be withdrawn at this time.

#### V. Responses to the Rejections under 35 U.S.C. § 103(a)

Claims 36-43 and 45-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh. Claims 36-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh, and further in view of Ambion.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

V.A. Response to the Rejection over Reich in view of Fosnaugh

Claims 36-43 and 45-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh. According to the Patent Office, Reich teaches *inter alia* siRNA molecules that target HIF-1 a mRNA and inhibit the expression of the HIF-1 $\alpha$  gene via RNA interference. The Patent Office concedes, however, that while Reich teaches utilizing nucleotide linker hairpin regions, this reference does not teach non-nucleotide linkers. Additionally, the Patent Office concedes that while Reich teaches modifying siRNA molecules to enhance resistance to nuclease digestion, the reference does not specifically teach phosphorothioate nucleotides, universal bases ribonucleotides, or acyclic nucleotides. The Patent Office asserts that Fosnaugh cures these deficiencies.

Without acquiescing to the contentions of the Patent Office in support of this rejection, applicants respectfully submit that claim 36 has been amended to recite a small interfering RNA (siRNA) molecule that down regulates expression of a human hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) gene by RNA interference comprising a sense region and an antisense region, wherein the sense region comprises the sequence 5'-GATGACATGAAAGCACAGA-3' (SEQ ID NO: 7) and the antisense region comprises a 100% reverse-complement of SEQ ID NO: 7. Applicants respectfully submit that as set forth hereinabove with respect to the rejection of claim 36 under 35 U.S.C. § 102(e) over Reich, this reference does not teach an siRNA with this sequence.

Applicants further respectfully submit that Reich does not suggest this sequence, which the Patent Office has also conceded given that this element was originally recited in claim 44, and claim 44 is not subject to this rejection.

Accordingly, applicants respectfully submit that claim 36 has been distinguished over Reich in view of Fosnaugh. Claims 37, 43, 60, and 61 have been canceled, and thus the instant rejection is believed to be moot as to these claims. As a result, applicants respectfully request that the instant rejection of claims 36, 38-44, 45-59, 62, and 63 be withdrawn at this time.

V.B. Response to the Rejection over Reich in view of Fosnaugh

Claims 36-63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh, and further in view of Ambion. According to the Patent Office, Ambion teaches a siRNA target finder and design tool and teaches that the algorithms followed the guidelines for siRNA design to generate a report indicating preferential sense and antisense siRNA oligonucleotides for a given mRNA sequence. The Patent Office thus contends that it would have been obvious to design a siRNA

with the preferable structural characteristics taught by Reich and Fosnaugh as discussed in the previous rejection wherein the sense region comprises instant SEQ ID NO: 7. The Patent Office further asserts that one would have been motivated to specifically design the siRNA targeted to HIF-1a of Reich to comprise instant SEQ ID NO: 7 because Ambion teaches an algorithm, wherein insertion of the published HIF-1 $\alpha$  sequence (GENBANK® accession number NM\_001530) results in the identification of hotspots and preferential siRNA sequences and specifically identified instant SEQ ID NO: 7 as a preferred target sequence.

Initially, applicants respectfully submit that claims 37, 43, 44, 60, and 61 have been canceled, and thus the instant rejection is believed to be moot as to these claims.

With respect to the rejection as applied to claims 36, 38-42, 45-59, 62, and 63, applicants respectfully submit that Reich in view of Fosnaugh, and further in view of Ambion does not support the instant rejection of these claims. Particularly, and without acquiescing to the contentions of the Patent Office in support of the rejection, applicants respectfully submit that none of the identified sequences are ones that produce an siRNA that comprise a sense region comprising SEQ ID NO: 7 and an antisense region comprising a 100% reverse-complement of SEQ ID NO: 7 as recited in claim 36.

To elaborate, the Patent Office depicts on page 16 of the Non-Final Official Action one of the sequences identified by the Ambion siRNA algorithm. It is noted that the depiction presented shows a sense sequence and an antisense sequence, as well as an alignment of the two. As shown in this alignment, the sense strand has the sequence 5'-GAUGCAUGAAAGCACAGA-3', and the antisense strand has the sequence 5'-UCUGUGCUUUCAUGCAUC-3'. It is noted that the sense and antisense strands displayed in this alignment are each 18 nucleotides in length. Applicants respectfully submit that SEQ ID NO: 7 is 19 nucleotides in length, and thus contrary to the Patent Office's assertion, the sequences identified by the Ambion siRNA algorithm do not comprise SEQ ID NO: 7. Thus, applicants respectfully submit that there is no suggestion in Reich in view of Fosnaugh, and further in view of Ambion to produce the subject matter of claim 36.

Accordingly, applicants respectfully submit that the combination of Reich, Fosnaugh, and Ambion does not support a rejection of claim 36 under 35 U.S.C. § 103(a). Claims 38-42, 45-59, 62, and 63 all depend from claim 36, and thus are also believed to be distinguished over the cited combination of references. As a result, applicants respectfully request that the instant rejection of claims 36, 38-42, 45-59, 62, and 63 under 35 U.S.C. § 103(a) be withdrawn at this time. Applicants further respectfully solicit a Notice of Allowance to that effect.

VI. Discussion of the New Claims

New claims 64 and 65 have been added. Support for the new claims can be found throughout the specification as filed, including particularly at page 13, line 26, through page 14, line 2, and in the Sequence Listing. Thus, no new matter has been added by the inclusion of the new claims.

Applicants respectfully submit that new claims 64 and 65 are believed to be distinguished over the cited references for the reasons set forth hereinabove with respect to claim 36. Accordingly, applicants respectfully submit that new claims 64 and 65 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

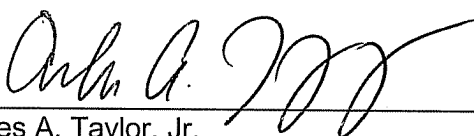
Deposit Account

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,  
JENKINS, WILSON, TAYLOR & HUNT, P.A.

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